Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797-805.

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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Supplementary Appendix

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SECTION 1. Structure of the NHLBI Heart Failure Clinical Research Network

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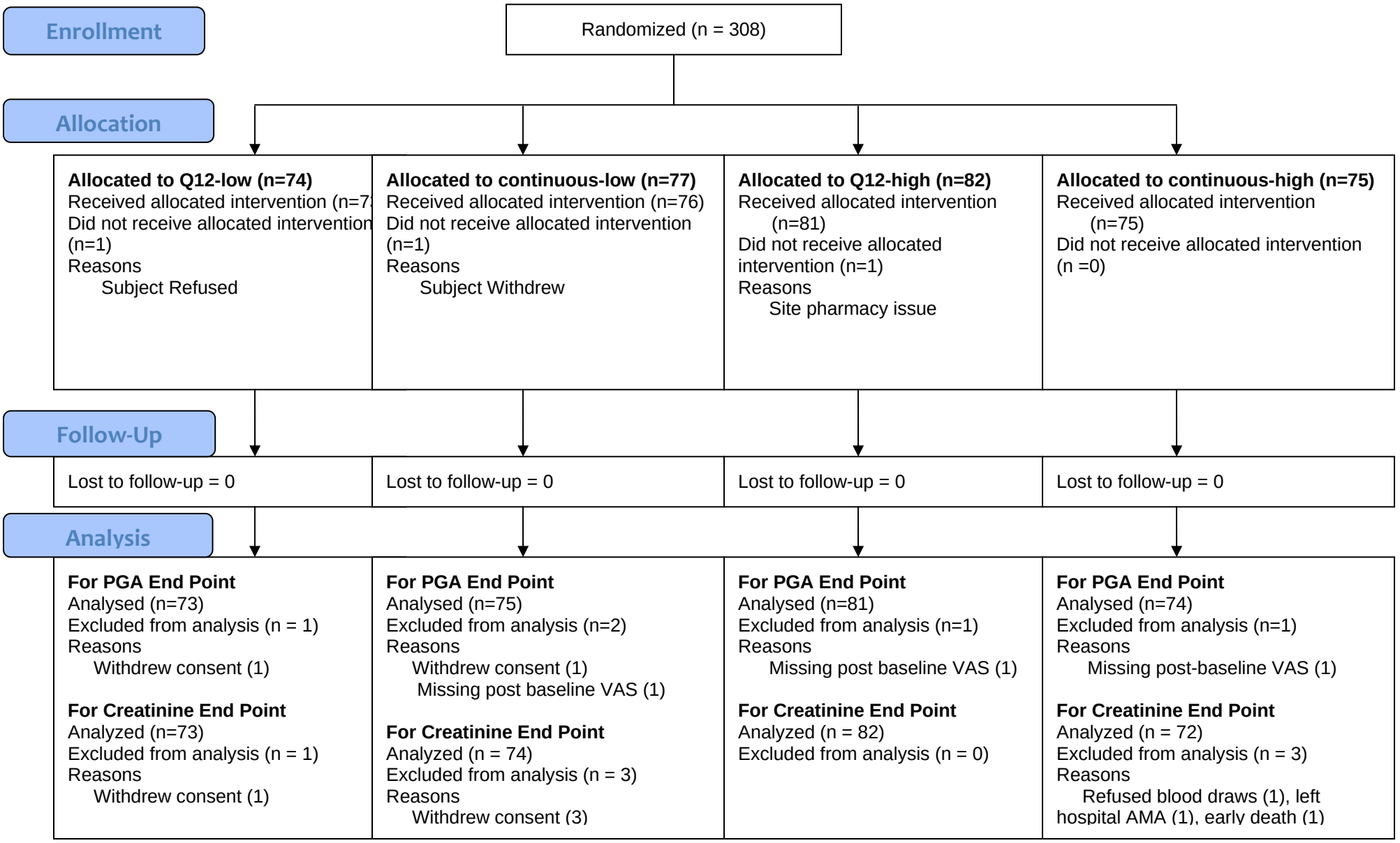
SECTION 2. Consort Diagram



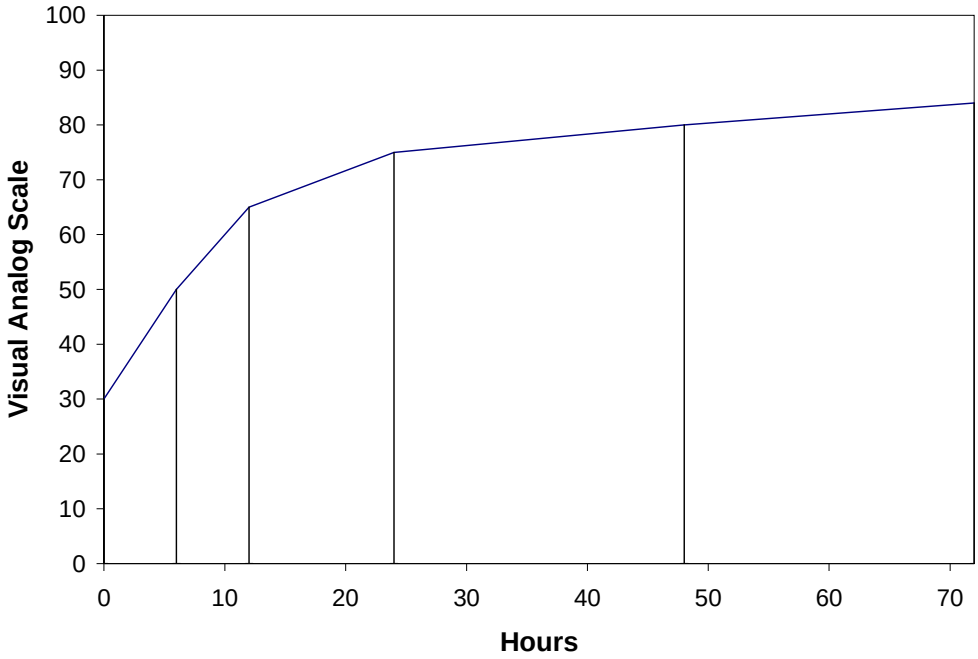
SECTION 3. Definitions of End Points

Assessment of Symptoms by Visual Analog Scale: Patient Global Assessment (PGA) and dyspnea

Patients were asked to self assess both their general well being (PGA) and their level of dyspnea using a visual analog scale (VAS) method. For PGA, patients marked their global well being on a 10 cm vertical line, with the top labeled “best you have ever felt” and the bottom labeled “worst you have ever felt”. For dyspnea, the labels were “I am not breathless at all” and “I am as breathless I have ever been”. The VAS was scored from 0 to 100 by measuring the distance in millimeters from the bottom of the line. The patient was unaware of the numerical value of their response. Patients self assessed both PGA and dyspnea at randomization, 6, 12, 24, 48, 72, and 96 hours.

Quantification of Area under the Curve

For each patient, a plot of the respective VAS score over time was constructed with points existing for each of the VAS measurements at baseline, 6 hours, etc. after randomization through 72 hours. A straight line was drawn connecting each of the points showing the trend over time. The area under the entire piecewise line is the response variable. A visual example is provided showing hypothetical data through 72 hours.



This area was determined by calculating the sum of the areas of each of the individual trapezoids. Each trapezoidal area was composed of the area bordered

by the time interval on the x-axis, the respective VAS score at each of the time points on the y-axis, and the line segment connecting the VAS scores between the two y-axis values. The number of trapezoids available depended on the completeness of the data. The VAS measurements may not have been measured exactly at the specified time points. For example, the measurement corresponding to the 12 hour time point may actually have been measured, for example, at 11 or 12.5 hours after randomization. In calculating the AUC, the baseline measurement was always set at the 0 time point. For the analysis time point at the end of the interval in question (e.g., 72 hours for the primary end point), the measurement time was set to the interval end point. For all of the interim measurement points, the exact time the measurement was obtained was used.

Rationale for Statistical Power Assumptions for PGA VAS

Calculation of sample size and statistical power requires estimating the minimum clinically important change (MCID). For the PGA VAS AUC, we estimated the MCID to be 600 points. This estimate was based on extrapolation from dyspnea measurements using the VAS AUC in a published registry by Ander [1] as well as in the VERITAS study [2]. Although these studies evaluated shorter time periods (2 hours and 24 hours), the MCID used in these two prior studies would extrapolate to approximately 756 and 450 points at 72 hours. Based on these data, we believe that a difference in VAS-AUC of 600 over the 72 hour treatment period represents a reasonable estimate of MCID.

Definitions of Composite End Points

Proportion of Patients Free of Congestion at 72 hours:

Freedom from congestion was defined as JVP < 8 cm, no orthopnea, trace peripheral edema or less

Worsening or persistent heart failure

Defined as the need for rescue therapy (additional open label loop diuretic, addition of thiazide, IV vasoactive agent for heart failure treatment, ultrafiltration, mechanical circulatory or respiratory support) over 72 hours after randomization

Development of Cardio-renal syndrome

Defined as an increase in serum creatinine > 0.3 mg/dl from randomization at any time point during 72 hours after randomization

Treatment Failure

Defined as the development of ANY ONE of the following during the 72 hours after randomization:

- development of cardio-renal syndrome as defined above
- worsening or persistent heart failure as defined above

- clinical evidence of over-diuresis requiring intervention (such as administration of IV fluids)
- death

SECTION 4. Serious Adverse Events (SAEs)

Number with data	Q12 (N=156)	Continuous (N=152)	P value	Low Dose (N=151)	High Dose (N=157)	P value
Serious SAE	44% (69)	44% (67)	0.92	50% (76)	38% (60)	0.033
Any Severe SAE's	23% (36)	24% (37)	0.80	25% (37)	23% (36)	0.75
Specific SAE's of Interest						
Cardiac SAE's	28% (43)	25% (38)		30% (46)	22% (35)	
Acute Myocardial Infarction	3% (4)	1% (1)		3% (4)	1% (1)	
Atrial Fibrillation	1% (1)	1% (2)		1% (2)	1% (1)	
Cardiac Arrest	2% (3)	2% (3)		2% (3)	2% (3)	
Ventricular Tachycardia	4% (7)	3% (4)		5% (7)	3% (4)	
Metabolic SAE's	5% (8)	6% (9)		7% (10)	4% (7)	
Gout	1% (1)	0% (0)		1% (1)	0% (0)	
Hyperkalaemia	1% (2)	4% (6)		2% (3)	3% (5)	
Hypokalaemia	1% (2)	1% (1)		1% (2)	1% (1)	
Hyponatraemia	1% (1)	1% (1)		1% (1)	1% (1)	
Renal and Urinary SAE's*	5% (8)	8% (12)		9% (13)	4% (7)	
Renal failure	5% (8)	8% (11)		9% (12)	4% (7)	
Renal failure requiring dialysis	1% (1)	3% (5)		2% (3)	2% (3)	
*"Renal failure" based on investigator SAE reporting. "Renal failure requiring dialysis" based on in hospital procedures during index hospitalization						

SECTION 5. Diuretic Administration

Pre-Randomization diuretics

DOSE enrolled patients within 24 hours of presentation with ADHF (median 14.6 hours). Most patients received treatment with IV diuretics prior to enrollment in DOSE. Median doses of loop diuretic received (in IV furosemide equivalents) in the 24 hour period prior to randomization are shown for each treatment group in the table below.

Median Diuretic Dose in 24 hours prior to Randomization (in IV furosemide equivalents)							
	Q12	**Cont.**	**P value**		**Low-dose**	**High-dose**	**P value**
Loop diuretic received in 24 hours prior to randomization (mg) Median (25^{th}, 75^{th})	80 (60, 160)	80 (40, 140)	0.40		80 (40, 160)	80 (60, 160)	0.76

Total diuretic received during randomization period

DOSE allowed for adjustment of randomized study treatment at 48 hours, as well as allowing the need for additional diuretics as "rescue therapy". Total diuretic dosage (median IV furosemide equivalents) received during the 72 hours between randomization and the assessment of the primary end points is shown below for each treatment comparison.

Median Loop Diuretic Received over 72 hours (in IV furosemide equivalents)							
	Q12	**Cont.**	**P value**		**Low-dose**	**High-dose**	**P value**
Study drug (mg) Median (25^{th}, 75^{th})	518 (292, 832)	406 (240, 628)	0.008		285 (200, 480)	688 (429, 1067)	< 0.0001
Open label loop diuretic (mg) Median (25^{th}, 75^{th})	80 (60,200)	95 (40, 160)	0.74		120 (60, 210)	80 (40, 160)	0.08
Total loop diuretic (mg) Median (25^{th}, 75^{th})	592 (370, 884)	480 (300, 773)	0.06		358 (238, 560)	773 (518, 1100)	< 0.0001

Thiazide diuretic use

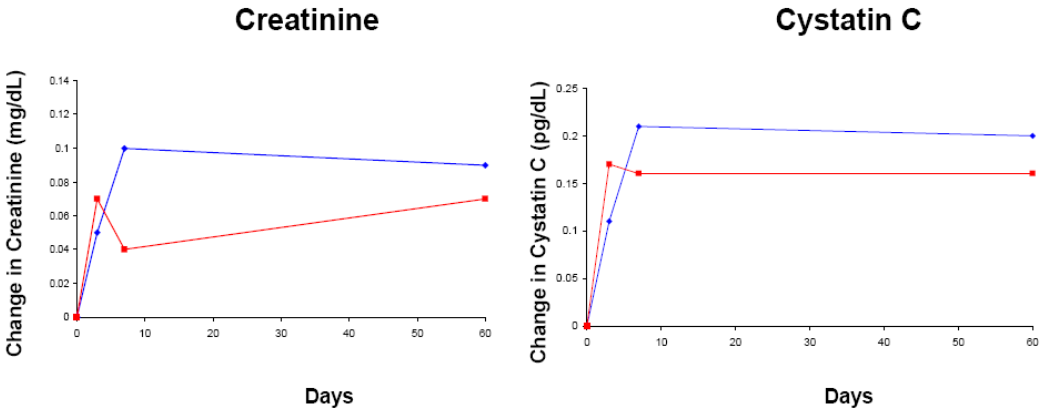
Thiazide diuretics were allowed in DOSE even given chronically. The need for the addition of a new thiazide diuretic during the 72 period of study drug treatment was considered as a treatment failure, which is summarized below.

	Q12	Cont.	P value		Low-dose	High-dose	P value
Thiazide added during the 72 hour treatment period (%, n)	16% (25)	7% (11)	0.02		15% (23)	8% (13)	0.06

SECTION 6. Changes in Renal Function over Time

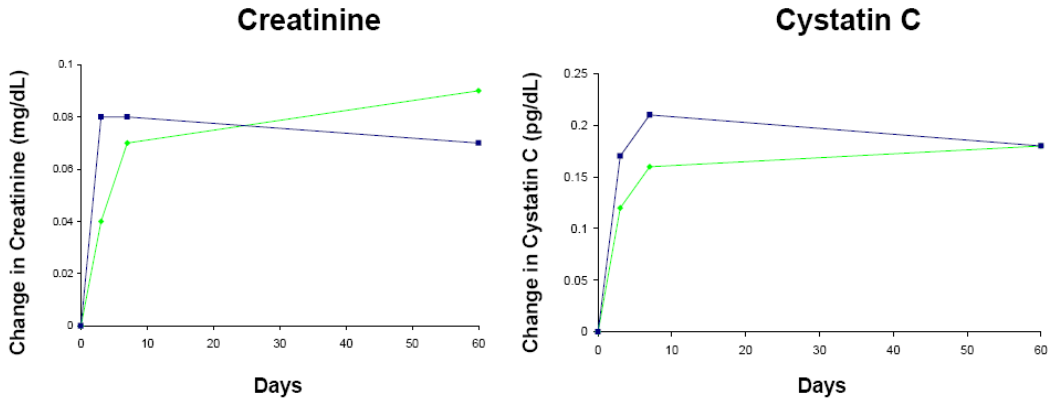
Changes in Renal Function over time for Q12 (blue line) vs. continuous (red line)

P > 0.05 for all timepoints



Changes in Renal Function over time for high dose (blue line) vs. low dose (green line)

P > 0.05 for all timepoints



SECTION 7. Clinical Outcomes

The table below shows the individual components of the composite clinical end point of emergency department visit, rehospitalization, or death within 60 days. All events are shown (i.e., a patient may have had more than one event).

	Q12	**Cont.**	**P value**	**Low-dose**	**High-dose**	**P value**
ED visit % (N)	11% (16)	15% (21)	0.29	11% (16)	14% (21)	0.51
Rehospitalization % (N)	33% (50)	29% (42)	0.49	36% (51)	27% (41)	0.10
Death % (N)	8% (13)	11% (16)	0.51	11% (14)	14% (15)	0.93

SECTION 8. References

1. Ander DS, Aisiku IP, Ratcliff JJ, Todd KH, Gotsch K. Measuring the Dyspnea of Decompensated Heart Failure With a Visual Analog Scale: How Much Improvement Is Meaningful? Congestive Heart Failure 2004;10:188-91.

2. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007;298:2009-19.